Acute on Chronic Liver Failure

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Acute on Chronic Liver Failure (ACLF)

- **Definition APASL:** acute hepatic insult in patient with (diagnosed or undiagnosed) chronic liver disease (without or with cirrhosis) causing bilirubin >/= 5 mg/dL and INR >/= 1.5, complicated within 4 weeks with ascites and/or PSE.
  - Is at high risk of extra-hepatic multisystem organ failure.
  - "Golden window", were therapy can be started, precedes multisystem organ failure.
    - In Asia 80% are due to HBV.
    - Nucleoside analogs improve mortality if HBV-DNA decrease > 2 log within 2 weeks.
  - Asks for early detection and treatment of cerebral failure (PSE I -IV, and ammonia >/=75 mM/L as threshold for cerebral edema) and renal failure (creatinine elevation >/= 0.3 mg/dL or >/= 1.5-fold over 48 h, or U.O. < 0.5 mL/kg/h for > 6 h).
  - Considers >/= 2 organ failures as high risk for 28-d mortality (bili >/= 10 can be one of them)

Acute on Chronic Liver Failure (ACLF)

- **Definition EASL-CLIF:**
  - **Acute decompensation (AD)** of chronic liver disease (without or with cirrhosis) with development of large ascites, PSE, GI hemorrhage and/or bacterial infection,
  - **associated with at least 2 organ failures**, with one being kidney with a creatinine > 1.5 mg/dL,
  - leading to a 28-day mortality >/= (15% in study) 22% (in reality).
- **Group at highest risk:**
  - Patients with compensated cirrhosis or recently decompensated cirrhosis in the last 3 months.
    - Patients without prior decompensation develop more severe ACLF

Organ Failure and Grading Definitions in ACLF

ORGAN FAILURE (% of ACLF)

- **Coagulation (28%):** INR > 2.5 or plat < 20K (mortality OR 6.8)
- **Kidney (56%):** Creat > 2 mg/dL or Hemodialysis (mortality OR 6.3)
- **Liver (44%):** Bili > 12 mg/dL (mortality OR 3.9)
- **Brain (24%):** HE III or IV (mortality OR 3.9)
- **Lung (9%):** SpO_2/FiO_2 </= 214 or PaO_2/FiO_2 < 200 (mortality OR 2.8)
- **Circulation (17%):** need of inotropes (mortality OR 2.2)

48% had >/= 2 organ failures

GRADES OF ACLF (% of AD)

- **ACLF-1 (16%):** (28-d mort 22.1%)
  - renal failure (creat > 2 mg/dL), or
  - nonrenal organ failure associated with:
    - creatinine 1.5-1.99 mg/dL and/or
    - grade I-II encephalopathy
- **ACLF-2 (11%):** 2 organ failures (28-d mort 32%)
- **ACLF-3 (4%):** 3-6 organ failures, (28-d mort 73%)

EASL-CLIF prognostic and diagnostic scores for ACLF

CLIF-C ACLF score for mortality prediction[1]*
10 x [0.033 x Clif OFs + 0.04 x Age + 0.63 x Ln(WBC) – 2]

Chronic liver failure – organ failure score system[1]			
Organ/system†	1 point	2 points	3 points
Liver (bilirubin, mg/dl)	<6	≥6–<12	**≥12.0**
Kidney (creatinine, mg/dl)	<2.0	**≥2.0–<3.5**	**≥3.5 or renal replacement**
Brain/HE (West Haven Criteria)	Grade 0	Grades 1–2	**Grades 3–4‡**
Coagulation (INR, PLT count)	<2.0	≥2.0–<2.5	**≥2.5**
Circulation (MAP, mmHg and vasopressors)	≥70	<70	**Use of vasopressors**
Lungs PaO_2/FiO_2, or	>300	≤300–>200	**≤200§**
SpO_2/FiO_2	>357	>214–≤357	**≤214§**

*Age in years, creatinine in mg/dL, WBC in 10^6 cells/L, sodium in mmol/L;
†Bold text indicates the diagnostic criteria for organ failures; ‡Patients submitted to mechanical ventilation due to HE and not to a respiratory failure were considered as presenting a cerebral failure (cerebral score = 3); §Other patients enrolled in the study with mechanical ventilation were considered as presenting a respiratory failure (respiratory score = 3)

1. Jalan R, et al. J Hepatol 2014;61:1038–47;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Triggers of ACLF

Modified from: Arroyo V et al. J Hepatol 2015;62:S131-s143

- Bacterial infection (39%) (most common SBP & pneumonia)
- Alcohol (23%)
- GI bleed (18%) (if causes jaundice & coagulopathy)
- Drug or Herbal therapy/CAM.
- AIH flare-up
- Wilson disease flare-up

Most common cause in children

- HBV flare-up (HBV-DNA > $2x10^4$ IU/mL)
- HEV
- HAV/HCV/HDV
- Non-bacterial Infection
- Sepsis
- TIPS
- Paracentesis without albumin
- Surgery
- Other
- No precipitating factor: 43%

More than 1 trigger in 30%

Sub-Types of ACLF

- By underlying Liver Disease Severity:
  - Type A: over Chronic liver disease without cirrhosis.
  - Type B: over Compensated Cirrhosis.
  - Type C: over Decompensated Cirrhosis
- By Trigger:
  - Infection related.
  - Non-infection related.

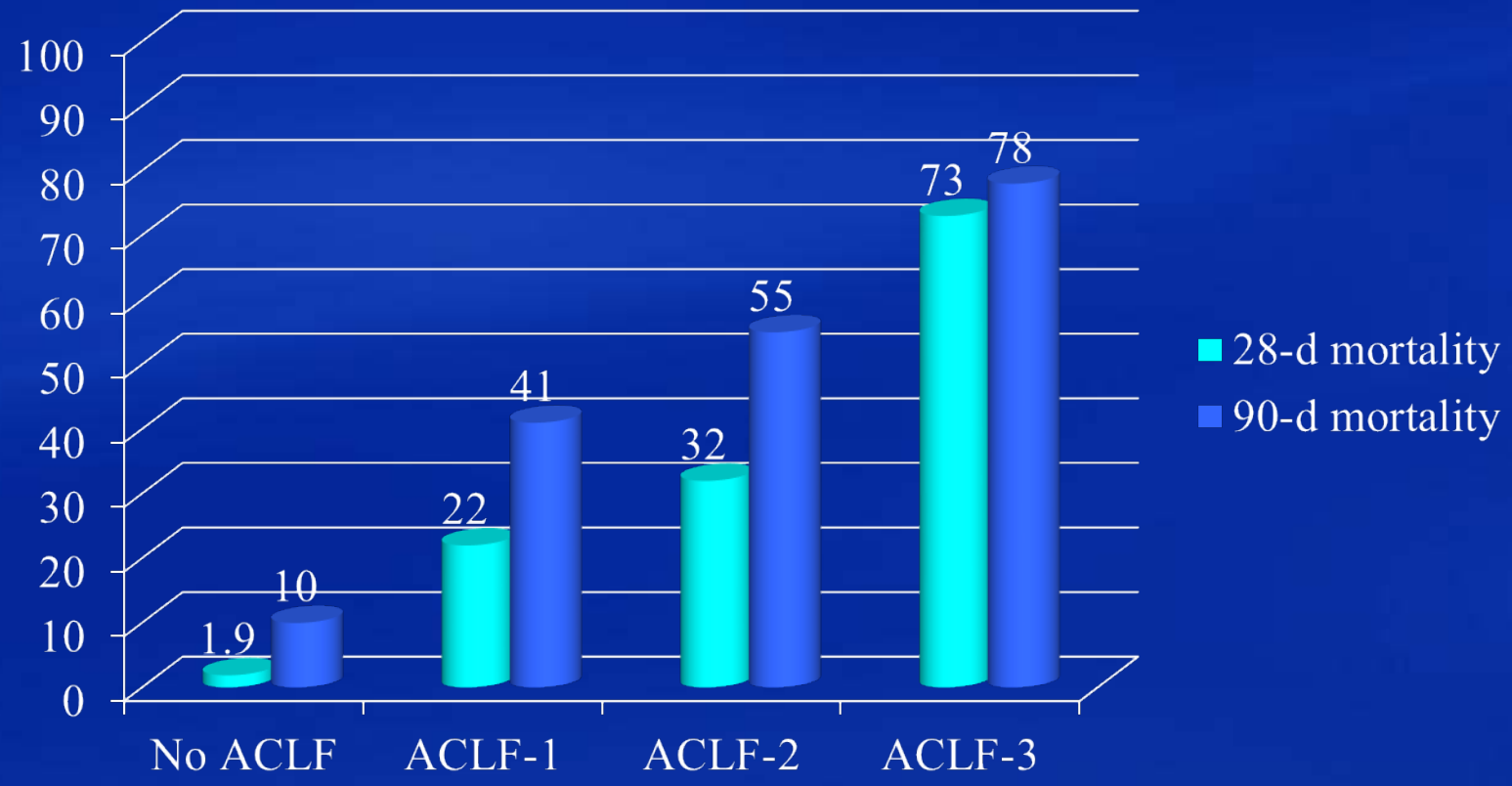
  - Hepatic injury (HAV, HEV, HBV, AIH, Wilson, alcohol, drug hepatotoxicity …)
  - Extra-hepatic injury (Infection, GI bleed, surgery, …)

Presentation and Evolution

- Of the patients with “acute decompensation” (AD):
  - Only 20-22.5% have ACLF at admission
    - 11% will develop ACLF during the hospitalization (31-33.5% of all AD patients)
  - 77.5% do not have ACLF at admission, and they have a 28day mortality of 4.7%
    - Mortality is 1.9% if they never develop ACLF (66.5% of all AD patients)
- Of patients with ACLF-1 at time of diagnosis (11% of AD),
  - 55% improved and survived, and
  - 30% worsened to ACLF-3.
- Of patients with ACLF-3 at time of diagnosis (3.5% of AD),
  - only 16% improved to “no ACLF” status.

Mortality of ACLF

28 and 90 days



Presentation and Evolution

- Bilirubin >/= 12 mg/dL at diagnosis of ACLF is an independent predictor of severity.
- Of the patients with ACLF, 48% will have >/= 2 organ failures.
- The prognosis of ACLF is most dependent of the early clinical course than on the initial grade;
  - 50% improve,
  - 30% have fluctuating or steady course, and
  - 20% worsen.
- Resolution in 40%:
  - ACLF-1: 55%, ACLF-2: 35%; ACLF-3: 16%
- Most patients who died progress to ACLF-3.
- Presence or absence of “precipitating event” does not affect mortality.

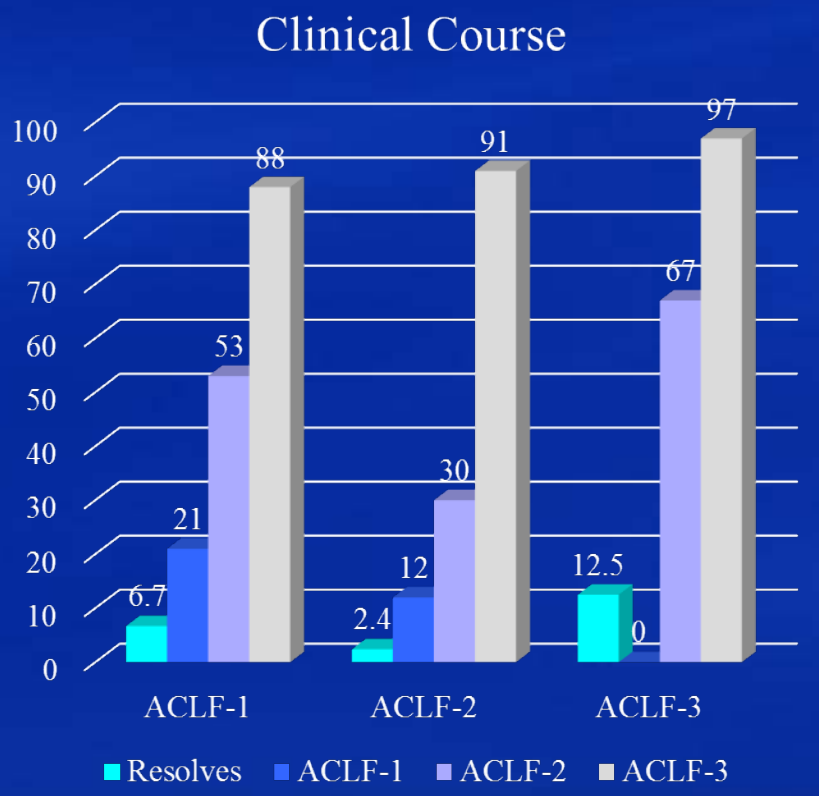
Clinical Course and Mortality of ACLF

Gustot T et al. Hepatology 2015;

Clinical Course

	Resolves	Improve	Steady or fluctuate	Worsen
ACLF-1	55%	N/A	24%	21%
ACLF-2	35%	14%	26%	26%
ACLF-3	16%	16%	68%	N/A

28-day Mortality (%)



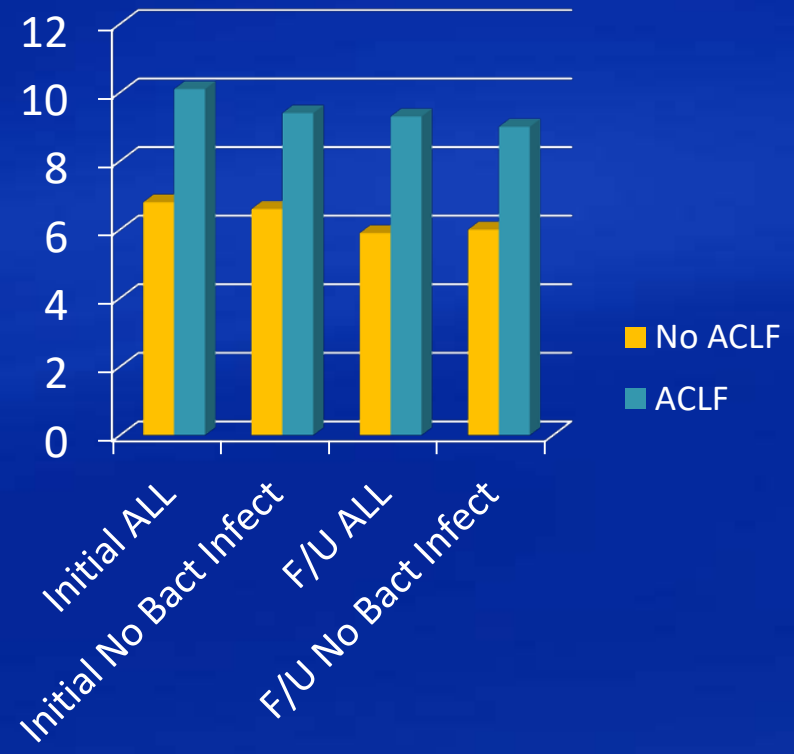
ACLF Evolving Concepts

- Infection-associated ACLF is the one with evidence of infection before admission or within 48 h of admission.
- 2 of 3 of ACLF are not associated with bacterial infection.
  - 43% have not recognized cause.
- Mortality is slightly lower in non-infection cases.
- Mortality @ 28-days is the same from extra-hepatic vs hepatic insult (48-50%)
- Later, extra-hepatic injury has higher mortality than hepatic injury:
  - 90-d mortality (68% vs 59%) and
  - 1-year mortality (75% vs 64%).
- Infected and Non-infected patients have high WBC and CRP (both even higher in infected ones) indicating **SYSTEMIC INFLAMMATION**.
- 81% of ACLF develop SIRS within 7 days (1 week window)
  - 24% by day 4 + 57% more by day 7.
- IS IMPORTANT TO RE-CALCULTE ACLF SCORE DAILY TO ASSES EVOLUTION AND THERAPY.

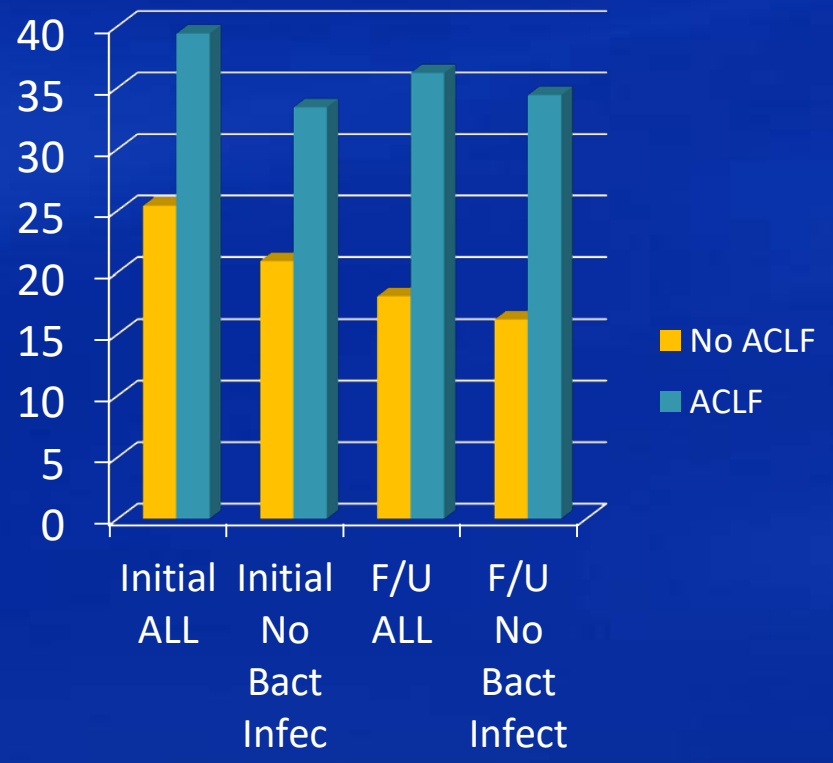
Leukocyte Count and CRP in CANONIC STUDY

Moreau R et al. J Clin Exp Hepatol 2014;5:81-85)

Leukocyte count
(x 10^9/L)



C-Reactive protein
(mg/L)



Inflammatory markers are high in ACLF compared with other Decompensated Cirrhosis

ACLF Evolving Concepts

- Mortality worsens with acquisition of any nosocomial infection (> 48 h after admission)
- Windows for therapy:
  - a) Best is before SIRS;
  - b) Before sepsis.
- In HRS, noradrenaline is better tolerated than terlipressin
- If AKI does nor improve, CRRT is better than SLED.
- Brain edema may occur in Hepatic Encephalopathy of ACLF; need to follow ammonia level to guide therapy.
- In MELD > 30 or refractory HRS-1, MARS or Helios may help as bridge to OLTx.
- Daily Monitoring of ACLF Score helps to asses evolution and response to therapy.

Prevention of ACLF

- Avoid infections, especially nosocomial infections:
  - PPI avoidance (increased risk of SBP & C difficile colitis)
  - Foley catheter avoidance
  - Minimization of duration and optimization of IV line management
  - Oral care (chlorhexidine)
- Avoid other known triggers of ACLF
  - Proper use of Albumin in LVP
  - Judicious use of antibiotic prophylaxis (d/c in past quinolone resistance)
  - Primary prophylaxis of esophageal variceal bleed.
  - Avoid hepatotoxins
  - Drug minimization
  - PPI avoidance as outpatient
  - Good compliance with drug therapy (AIH, HBV, Wilson)
  - Recognition & management of HBc(+) and HBsAg before immunosuppression

Algorithm for Management of Acute Decompensation

- Evaluate for evidence of ACLF by using the ***ACLF Calculator***;
- If ACLF, move to ICU for Intensive therapy or Transfer to Transplant Center.
- If no ACLF, then calculate the CLIF-C Acute Decompensation Score.
- ***CLIF-C Acute Decompensation Score*** can assist in management, when ACLF is not present:
  - If </= 45 (< 2% 3-month mortality) consider early discharge;
  - If 46-59 (2-30% 3-month mortality) needs hospital care in ward;
  - If >/= 60 (> 30% 3-month mortality) consider ICU and/or Transplant center transfer due to high risk of progression to ACLF

- http://www.clifresearch.com/ToolsCalculators.aspx

	DATA	SCORES
Bilirubin	☐ mg/dl	Liver score ☐ Liver failure ○ Yes ○ No
Creatinine	☐ mg/dl	Kidney score ☐
Renal replacement therapy	○ Yes ○ No	Renal failure ○ Yes ○ No
Use of vasopressors (Hepatorenal syndrome indication)	○ Yes ○ No	
West-Haven grade for HE	○ 0 ○ 1 ○ 2 ○ 3 ○ 4	Brain score ☐ Cerebral failure ○ Yes ○ No
INR	☐	Coagulation score ☐ Coagulation failure ○ Yes ○ No
MAP	☐ mm/Hg	Circulation score ☐
Use of vasopressors (Circulatory failure indication)	○ Yes ○ No	Circulation failure ○ Yes ○ No
Select one ◉ **PaO_2** (preferred) ○ **SpO_2**	☐	Lung score ☐ Respiratory failure ○ Yes ○ No
FiO_2	☐ %	
Mechanical Ventilation	○ Yes ○ No	
		Total Number Failures ☐ CLIF Organ Failure Score ☐
		ACLF Grade ☐

CLIF-C AD Score and expected mortality rates

Patients with Acute Decompensation and no ACLF

	DATA	SCORES
Age	years	
White-cell count	10^9cells/L	
Creatinine	mg/dl	
INR		
Sodium (Na)	mmol/L	
		CLIF-C AD Score
		Probability of dying at 1 month %
		Probability of dying at 3 month %
		Probability of dying at 6 month %
		Probability of dying at 12 month %

Reset Compute

The CLIF Consortium ACLF Score (CLIF-C ACLF)

- CLIF-C ACLF Score = 10 x [0.33 x CLIF-OFs + 0.04 x Age + 0.63 x ln (WBC count) – 2]
- The probability of death (P) at time “t” is:
  - $P = 1 - e[-CI(t) \times \exp(\beta(t) \times \text{CLIF-C ACLFs})]$
- http://www.clifresearch.com/ToolsCalculators.aspx

Therapy of ACLF

- Transfer to Transplant Center (if transplant candidate)
- ICU management
- Treat HRS early (monitor urine output and creatinine)
- Monitor Circulatory and Respiratory function.
- Correct intravascular depletion while avoiding excessive fluids.
- Monitor ACLF Score.
- Monitor brain function and ammonia:
  - treat HE,
  - intubate in HE grade III or IV,
  - high suspicion index for brain edema/ Intracranial HTN.

Therapy of ACLF

- Guided antibiotic use with narrowing of spectrum once sensitivity is known
- Intense enteral nutrition
- G-CSF for selected patients:
  - Not studied in patients with sepsis, multiorgan failure nor HE III or IV
  - Usually given as soon as ACLF-2 is reached or if Bili >/= 12 mg/dL.
- Selective use of MARS/Prometheus (as bridge to Liver Tx)
  - Does not improve survival over standard medical therapy (Br J Surg. 2011 May;98(5):623-31)
- Liver Transplantation. if Transplanted:
  - 1-year survival is 80%;
  - high mortality while waiting (overall mortality 50%);
  - mean waiting time: 11 days

G-CSF Use

(Shiv Kumar Sarin)

- Contraindications for g-CSF
  - Sepsis, severe sarcopenia, severe anemia; AKI?
  - Macrophage activation syndrome
  - Ferritin > 1000 ng/mL, high LDH, skin with “slate gray color”
  - Plasmapheresis
- Predicting good response to g-CSG
  - BM Bx with:
    - high osteoblasts,
    - high CD34,
    - low vascularity,
    - low perivascular fibrosis,
    - high Hematopoietic Stem Cells (HSC), Multi Potential Progenitors (MPP), and Common Myeloid Progenitors (CMP).

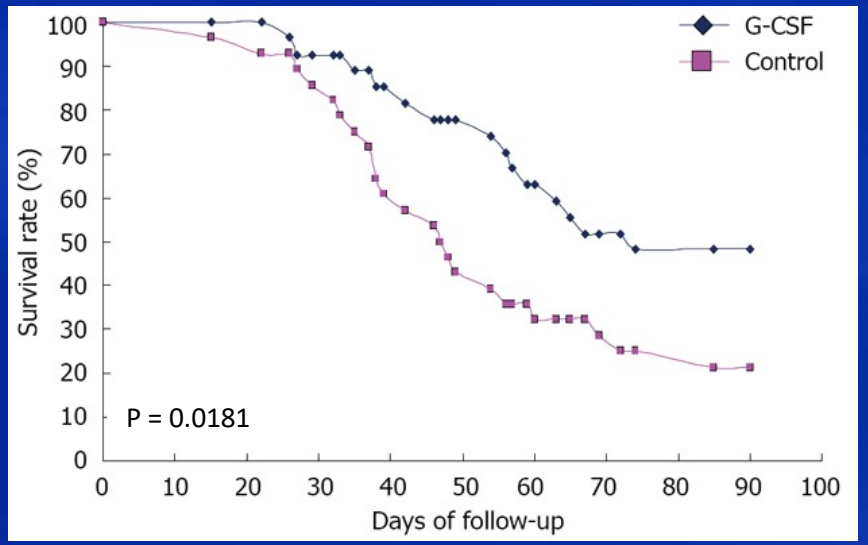
Granulocyte-colony stimulating factor therapy improves survival in patients with hepatitis B virus-associated acute-on-chronic liver failure

Duan XZ et al. World J Gastroenterol 2013 Feb 21;19(7):1104-10

g-csf 5 mcg/kg/d SQ x 6 days vs Placebo (+ Entecavir in all)

Parameters	G-CSF group (27)	Control group (28)	*P* value
Gender (male %)	22 (81.5)	22 (78.6)	0.755
Age (yr)	43.5 (29-63)	45.9 (22-65)	0.332
WBC (10^9/L)	5.79 ± 1.81	6.61 ± 1.71	0.443
Neutrophil (10^9/L)	3.53 ± 1.46	3.82 ± 1.17	0.114
Platelets (10^9/L)	182 (147-215)	174 (149-175)	0.680
ALT (U/L)	276 (197-801)	252 (189-1239)	0.430
AST (U/L)	246 (195-788)	251 (187-980)	0.544
Total bilirubin (mg/dL)	20 (11-30)	19 (10.5-30)	0.605
Cr (mg/dL)	1 ± 0.2	1 ± 0.6	0.475
INR	2.11 ± 0.28	2.34 ± 0.34	0.606
ALB (g/L)	29.11 ± 4.05	28.75 ± 4.63	0.596
HBV DNA ($\log_{10}$)	5.11 ± 1.37	5.55 ± 1.59	0.280
CTP score	12.17 ± 1.47	12.25 ± 1.29	0.349
MELD score	25.11 ± 3.30	26.30 ± 4.12	0.588

SURVIVAL



G-CSF therapy promoted CD34(+) cell mobilization in patients with HBV-associated ACLF, and improved the liver function and the survival rate of these patients.

Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure

Garg V et al Gastroenterology 2012 Mar;142(3):505-512

Parameters	Group A (n = 23)	Group B (n = 24)	*P* value
Male/female	20/3	21/3	.71
Age (*y*)	40 (30–65)	40 (19–55)	.70
Ascites	23 (100)	24 (100)	1
Total leukocyte count ($\times 10^3/mm^3$)	10.7 (3.9–22.1)	11.8 (3.8–28.7)	.34
Creatinine (*mg/dL*)	0.8 (0.5–3.7)	1.0 (0.3–4.9)	.06
Bilirubin (*mg/dL*)	25.6 (9.0–43.5)	23.9 (6.2–36.1)	.53
INR	2.20 (1.66–3.92)	2.71 (1.70–4.53)	.12
Encephalopathy	5 (10.6)	8 (17)	.51
Grade of encephalopathy	2 (1–2)	2 (1–2)	.28
Grade of varix (n = 42)	2 (0–3) (n = 22)	2 (0–4) (n = 20)	.32
Grade of varices ≥2	15 (65.2)	17 (70.8)	.76
Hepatorenal syndrome	4 (8.5)	5 (10.6)	1
HBV DNA $\log_{10}$ (*IU/mL*) (n = 11)	5.34 (5.04–6.60) (n = 4)	5.50 (4.76–7.93) (n = 7)	.91
HVPG (*mm Hg*) (n = 21)	16 (13–28) (n = 11)	19.25 (11–30) (n = 10)	.32
Fibrosis score (modified Ishak) (n = 18)	4 (0–5) (n = 10)	4 (0–4) (n = 8)	.237
CTP score	12 (11–14)	12 (10–14)	.91
MELD score	29 (21–40)	31.5 (20–40)	.069
SOFA score	5 (4–9)	6 (4–10)	.40

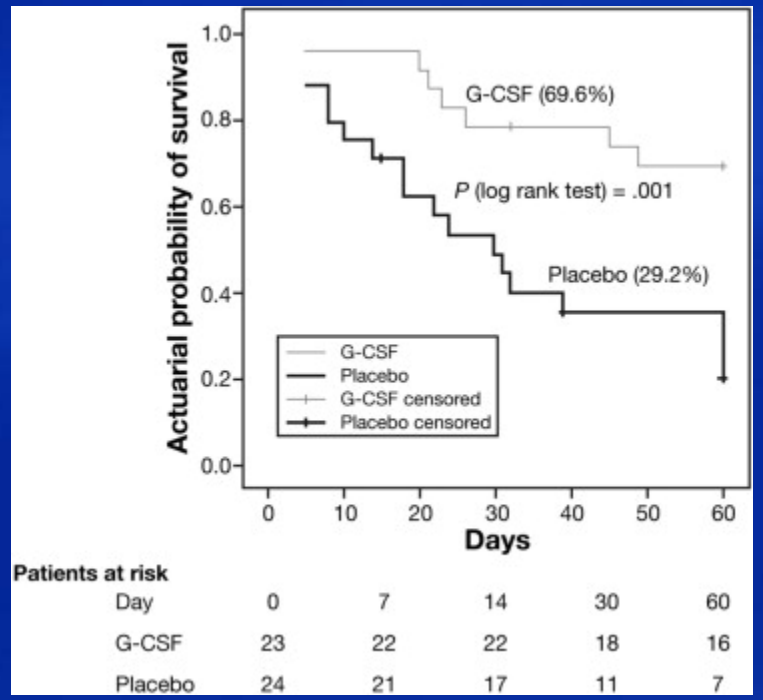
Acute event	Group A	Group B
Alcoholic hepatitis	15 (65)	12 (50)
Reactivation of hepatitis B virus	4 (17)	6 (25)
Antitubercular therapy	2 (9)	1 (4)
Hepatitis E virus infection	1 (4)	2 (8)
Cryptogenic	1 (4)	3 (12)
Underlying chronic liver disease		
Alcoholic liver disease	17 (74)	12 (50)
Hepatitis B	4 (17)	7 (30)
Cryptogenic	2 (9)	4 (16)

Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure

Garg V et al Gastroenterology 2012 Mar;142(3):505-512

Survival

[g-csf 5 mcg/kg/d x 5 d; then q 3rd d x 7 more doses] vs [Placebo]



Considerations + Conclusion

- Patients with HCC or sepsis were excluded.
- **The percentages of patients who developed hepatorenal syndrome, hepatic encephalopathy, or sepsis were lower in the g-csf group than in the placebo group (19% vs 71% [*P* = .0002], 19% vs 66% [*P* = .001], and 14% vs 41% [*P* = .04], respectively**
- **Survival was higher in the g -csf group (69.6 %) than in the placebo group (29.2%)**

Granulocyte Colony-Stimulating Factor in Severe Alcoholic Hepatitis: A Randomized Pilot Study

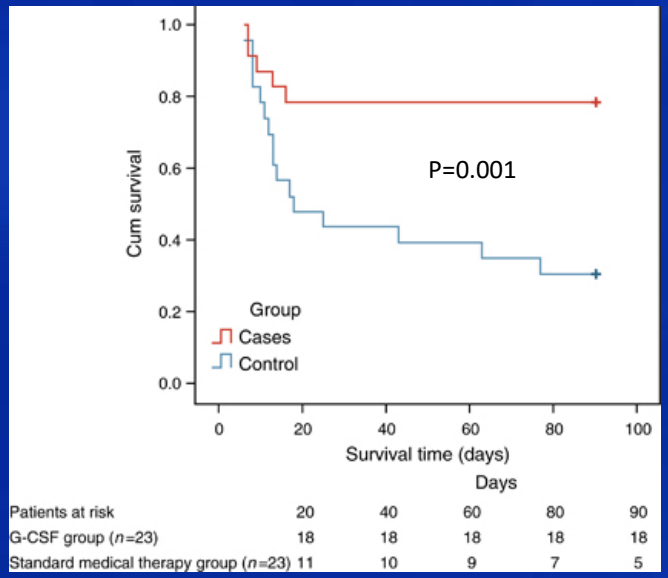
Singh V et al. Am J Gastroenterol 2014 Sep;109(9):1417-23

g-csf 5 mcg/kg BID SQ x 5 d vs Placebo
(All had Pentoxifylline 400 TID + Nutrition)

Variables	Group A (G-CSF; *n*=23)	Group B (SMT; *n*=23)	*P* value
Age (years)	41.7±7.5	44.3±13	0.417
Sex (M/F)	23:0	23:0	
Duration of symptoms before admission (days)	13.6±5.3	16.1±8.4	0.395
Total leukocyte count (/mm^3)	13,735±8,680	17,830±9,770	0.140
Platelets (/mm^3)	143,050±74,500	171,430±77,280	0.211
Bilirubin (mg/dl)	20.1±11.5	20.0±11.4	0.994
Alanine aminotransferase (IU/l)	101±41	136±95	0.118
Alkaline phosphatase (IU/l)	124±50	137±73	0.484
Albumin (g/dl)	3.0±0.7	2.8±0.5	0.437
Prothrombin time (s)	31.1±14	27.9±7.2	0.33
International normalized ratio	2.5±1.2	2.3±0.9	0.523
Sodium (mEq/dl)	135±8	135±9	0.762
Serum creatinine (mg/dl)	1.04±0.50	1.25±0.41	0.138
CTP score*	12	12	0.403
mDF score*	85.5	79.2	0.398
MELD score*	27	30	0.538
CD34$^+$ cells	0.31±0.45	0.15±0.2	0.51

Excluded HCC, uncontrolled infection, Portal V. thrombosis, previous corticosteroid use.

Survival + Conclusion



G-CSF is safe and effective in the mobilization of hematopoietic stem cells and improves liver function as well as survival in patients with severe alcoholic hepatitis

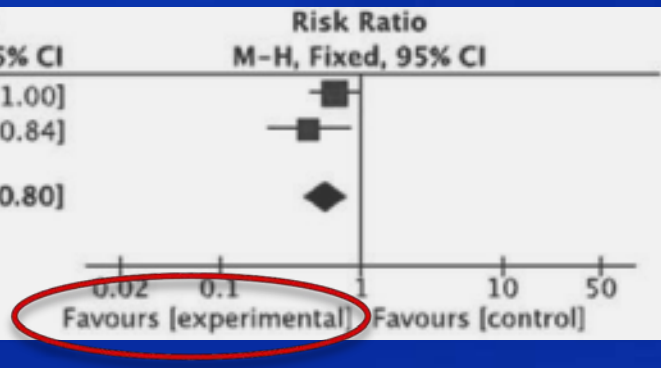
Granulocytecolony stimulating factor for acute-on-chronic liver failure: systematic review and meta-analysis of randomized control trials

Omelas-Arroyo VJ et al

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
DUAN2013	14	27	22	28	56.5%	0.66 [0.44, 1.00]
GARG2012	7	23	17	24	43.5%	0.43 [0.22, 0.84]
Total (95% CI)		**50**		**52**	**100.0%**	**0.56 [0.39, 0.80]**
Total events	21		39			

Heterogeneity: $Chi^2 = 1.21$, $df = 1$ ($P = 0.27$); $I^2 = 18\%$

Test for overall effect: $Z = 3.17$ ($P = 0.002$)



CONCLUSION

- The concepts of ACLF are in evolution.
- It is important to recognize ACLF due to its high mortality.
- The most important intervention is to prevent ACLF.
- The treatment of ACLF is not well defined, but they benefit from ICU management and early Liver Transplant evaluation.
- The use of C-CSF is beneficial to a sub-group of these patients.